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A chiral tellurium ferrocene as a chiral agent in NMR enantiomeric purity determination

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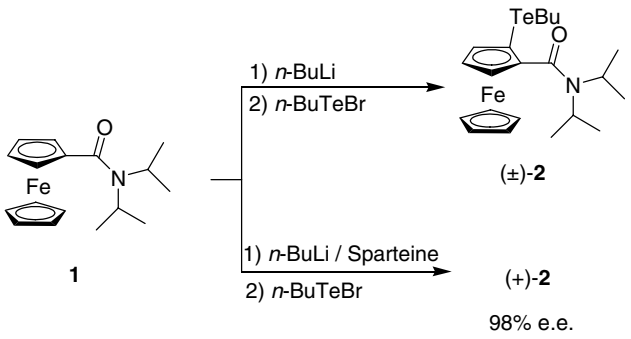
Abstract—The tellurium nuclear magnetic resonance spectrum of chiral tellurium ferrocene **2** produces a single signal at different chemical shifts when solubilized together with different enantiomeric proportions of chiral compounds.

1. Introduction

Over the last few decades, organic tellurium compounds have been applied as ligands in transition metal chemistry,[1] polymerization catalysts,[2] anti-oxidant agents,[3] and synthetic intermediates.[4] Notwithstanding this great development of the field, concern about the chirality of organic tellurium compounds has not been appropriately addressed. Few enantioselective synthetic methods involving chiral organic tellurium compounds have been reported.[5] Some time ago, we reported the synthesis of tellurium ferrocene **2**, which exhibits planar chirality, by deprotonation of the monosubstituted ferrocene **1** with *n*-butyllithium, followed by reaction with *n*-butyltellurenyl bromide. This reaction sequence gave a racemic mixture of **2**. When the deprotonation step was performed in the presence of (−)-sparteine, compound (+)-**2** was obtained in 98% ee[6] (Scheme 1).



Scheme 1.

The two enantiomers of (±)-**2** could be discriminated by ^{125}Te NMR when the spectrum was acquired in the presence of enantiomerically pure compounds such as menthol and (*S*)-(+)-*N*-(3,5-dinitrobenzoyl)-α-methyl-benzylamide **3** [*S*-(+)-*N*-DNBMBA].[7]

This phenomenon is noteworthy, since the discrimination of enantiomers and the determination of the enantiomeric purity of a sample has been a challenge to the scientific community over the last two centuries.[8]

Among the several techniques available for determining the enantiomeric excess of organic molecules, nuclear magnetic resonance has become an important method.[9] Despite its blindness to chirality, this technique is able to discriminate between enantiomers by producing a change in the environment of the compound to be analyzed by means of an auxiliary chiral compound.[10] This change generates different spectral data for the new diastereomeric compounds. In this type of discrimination, usually employing hydrogen detection, at least two signals are required and the integration of these signals can determine the enantiomeric excess. Since the hydrogen signals of organic compounds

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are constrained to a small spectral width, very often the overlaped signals cannot be properly integrated.[11] Conversely in ^{125}Te NMR spectroscopy, the spectral width is very large, and normally few signals with a reasonable separation are observed.[12]

The above mentioned preliminary observation that a racemic mixture of **2**, solubilized in the presence of an enantiomerically pure compound, gives two signals at different chemical shifts in the ^{125}Te NMR spectrum, suggested to us that organic tellurium compounds could be used as sensors to detect different magnetic environments.

Herein we found that an enantiomeric excess can be determined simply by the ^{125}Te NMR chemical shift of (+)-**2**, when its spectrum is run in the presence of the chiral compound to be analyzed.

2. Results and discussion

Initially the ^{125}Te NMR spectrum of racemic **2** was registered in CH_2Cl_2 in the presence of (*S*)-(+)-*N*-DNBMBA (*S*)-(+)-**3**. Two signals of equal intensity were observed at 327.8 ppm and at 328.9 ppm using diphenylditelluride as an external reference (Fig. 1b). By using a sample enriched in (+)-**2**, under the same conditions two signals of different intensity were observed. At 328.9 ppm a more intense signal was observed, which was attributed to a diastereomeric complex between (+)-**2** and (−)-**3**. At 327.8 ppm a less intense signal was observed, which was attributed to a diastereomeric complex between (−)-**2** and (−)-**3**. Integration of the peaks gave a 85:15 ratio (Fig. 1a). Repetition of the experiment using the same sample of (+)-**2** and (+)-**3** gave also two peaks in a 85:15 ratio at 327.8 and 328.9 ppm, respectively (Fig. 1c). These signals were attributed, respectively, to the (+)-**2**/(+)-**3** and (−)-**2**/(+)-**3** diastereomeric complexes.

As Figure 1 clearly shows, an inversion in the chemical shift was observed for compounds (+)-**2** and (−)-**2** when ligand (−)-**3** was changed for (+)-**3**. From these results we wondered if a ^{125}Te NMR analysis of enantiomerically pure (+)-**2** could be used to discriminate between the enantiomers of a (±)-mixture of **3**. However, a single signal in the ^{125}Te NMR spectrum was observed when (+)-**2** was exposed to any ratio of (±)-mixtures of **3**. All attempts to resolve the signals of ^{125}Te NMR, using different solvents and temperatures failed.

A preliminary check of these analyses led us to conclude that the excess of (*S*)-(+)-*N*-DNBMBA (*S*)-(+)-**3** was shifting the signal of the major enantiomer (+)-**2** to lower frequencies (to the right) and the excess of (*R*)-(−)-*N*-DNBMBA (*R*)-(−)-**3** was shifting the signal to higher frequencies (to the left) when compared to the signal of its racemate. This shift appeared to be proportional to the enantiomeric excess of (*R*)-(−)- or (*S*)-(+)-*N*-DNBMBA **3**. Since the chemical shift of the ^{125}Te NMR is extremely sensitive to small changes in concentration and temperature,[12] only after rigorous control of these variables this hypothesis could be confirmed (Fig. 2).

As far as we know, this is the first time that this observation has been reported, where a fast dynamic interaction between a chiral tellurium ferrocene **2** with some mixture of a chiral organic compound results in a single sharp resonance peak observed at a position that is the population weighted average of the chemical shifts, and corresponds to the enantiomeric excess of that mixture.

Figure 3 incorporates a graph showing the correlation between the ^{125}Te NMR chemical shift of (+)-*N*,*N*-diisopropyl-(2-butyltellurium)-ferrocenyl-carboxamide (+)-**2** and the enantiomeric excess of *N*-DNBMBA **3**. This graph was plotted using five different samples (a–e) carefully prepared by weighing and mixing the correct amounts of

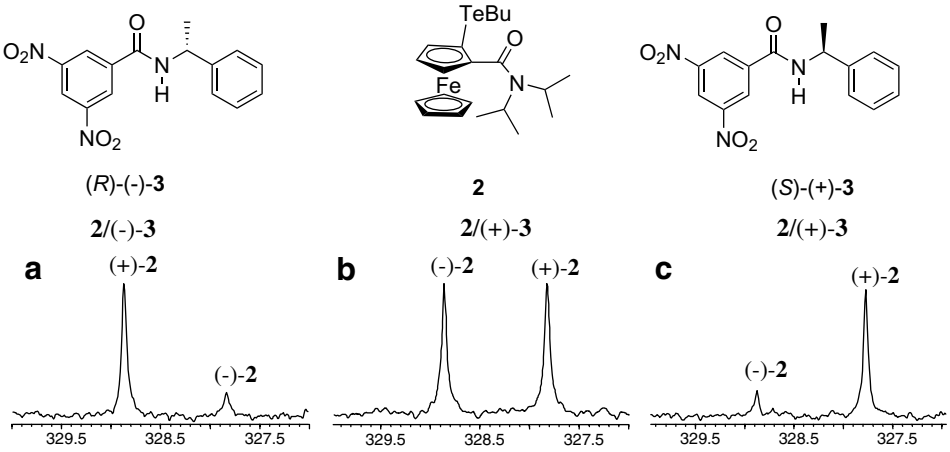

Figure 1. ^{125}Te NMR spectra of enriched enantiomeric mixtures of *N*,*N*-diisopropyl-(2-butyltellurium)-ferrocenyl-carboxamide **2** with: (a) (*R*)-(−)-*N*-DNBMBA **3**; (b) racemate of **2** with (*S*)-(+)-*N*-DNBMBA **3** and (c) (*S*)-(+)-*N*-DNBMBA (**3**). All experiments were recorded at 273 K on a Bruker AVANCE 400 spectrometer operating at 9.4 T, observing ^{125}Te at 126.3 MHz, using a $\pi/2$ pulse sequence and hydrogen decoupling only during the acquisition time. The chemical shifts are given in ppm, related to the external reference $(PhTe)_2$ in $CDCl_3$ at 422.0 ppm. All samples were prepared with 1 equiv of compound **2** and 2 equiv of the corresponding **3** solubilized in 0.5 mL of dichloromethane.

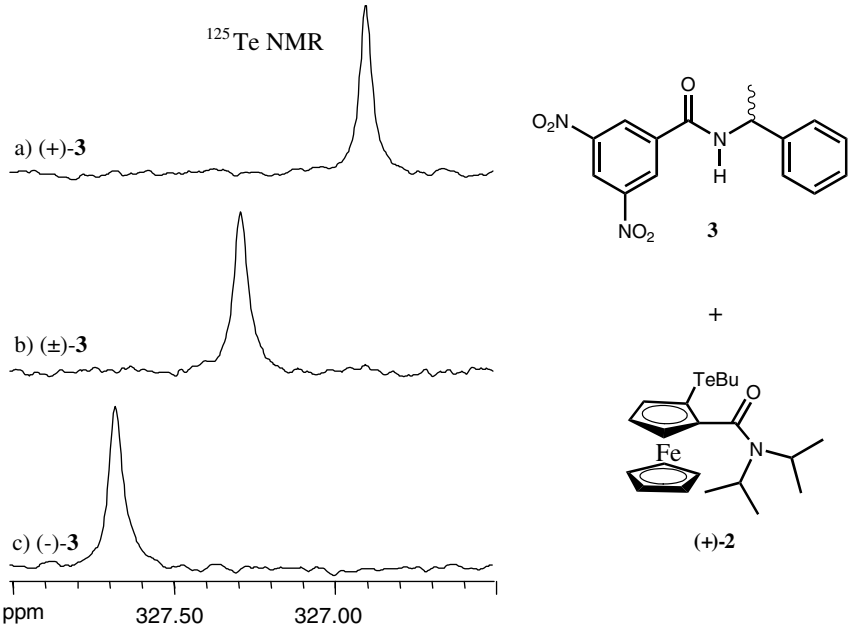

Figure 2. ^{125}Te NMR analysis of (+)-*N*,*N*-diisopropyl-(2-butyltellurium)ferrocenyl-carboxamide (+)-**2** under the same conditions described in Figure 1, but employing 9 equiv (to facilitate the weighing) of *N*-DNBMBA **3**: (a) (*S*)-(+)-*N*-DNBMBA (+)-**3**; (b) *N*-DNBMBA (±)-**3** as racemate and (c) (*R*)-(−)-*N*-DNBMBA (−)-**3**.

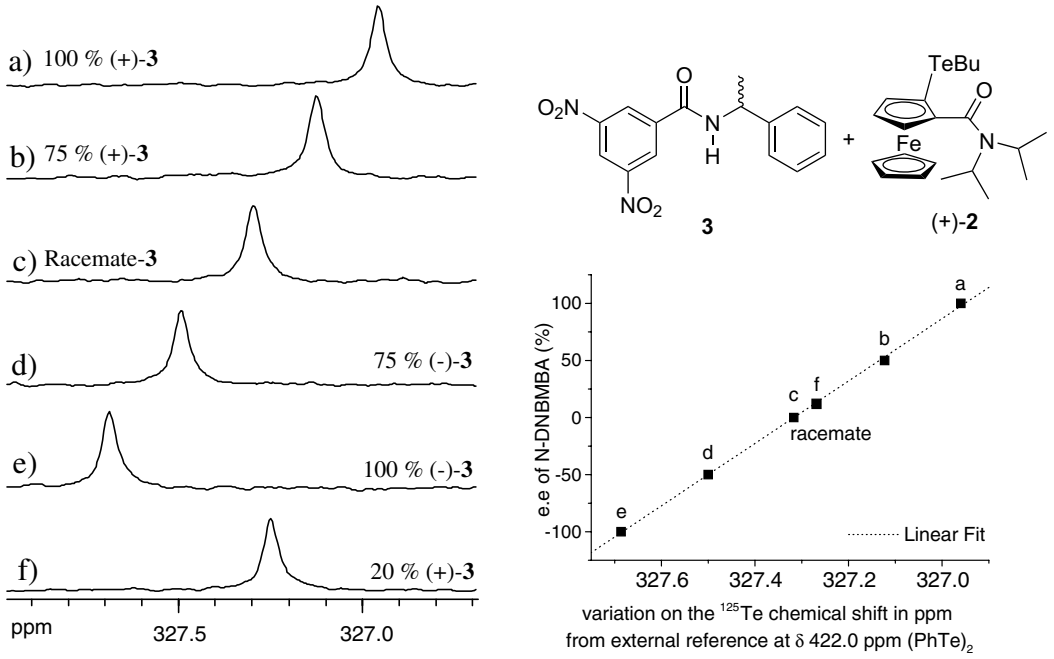

Figure 3. Graph showing the correlation between the ^{125}Te NMR chemical shifts of (+)-**2** and the enantiomeric excess of *N*-DNBMBA: (a) 100% ee of (*S*)-(+)-*N*-DNBMBA **3**; (b) 75% ee of (*S*)-(+)-*N*-DNBMBA **3**; (c) racemate of *N*-DNBMBA **3**; (d) 75% ee of (*R*)-(−)-*N*-DNBMBA **3**; (e) 100% ee of (*R*)-(−)-*N*-DNBMBA **3**; (f) employing the calibration curve with coefficient of linearity of 0.99969, sample f was calculated as 20% ee of (*S*)-(+)-*N*-DNBMBA **3**. All samples were prepared by weighing 1 equiv of (+)-**2** and 9 equiv of the correct mixture of each enantiomer of *N*-DNBMBA **3** to produce the desired enantiomeric excess, under the same conditions as described in Figure 1.

enantiomers of *N*-DNBMBA **3**. A straight line was obtained. A sample prepared with unweighed amounts of both enantiomers was submitted to the same analysis and the observed chemical shift is ploted in the graph of Figure 3. From this graph, the enantiomeric excess of **3** was determined as being 20%. This enantiomeric excess was confirmed by liquid gas chiral chromatography.

Besides *N*-DNBMBA **3**, menthol was employed, but for this compound the difference in chemical shifts was smaller

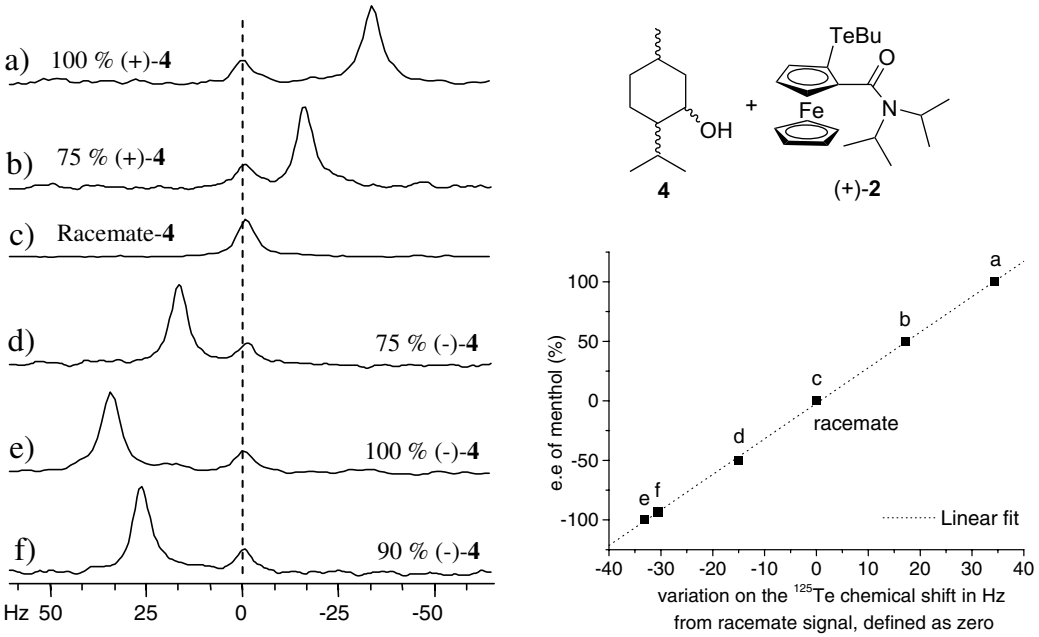

Figure 4. Graph showing the correlation of ^{125}Te NMR chemical shift of compound (+)-**2** (more intense) related to (−)-**2** (less intense) with the enantiomeric excess of menthol: (a) 100% ee of (+)-menthol (**4**); (b) 75% ee of (+)-menthol **4**; (c) racemate of menthol **4**; (d) 75% ee of (−)-menthol **4**; (e) 100% ee of (−)-menthol **4**; (f) employing the calibration curve with coefficient of linearity of 0.99963, sample f was calculated as 90% ee of (−)-menthol **4**.

(~0.25 ppm) than in the preceding case. To solve this problem, a new methodology using the sample enriched in (+)-**2** was developed. The ^{125}Te NMR signal of the minor enantiomer (−)-**2** in all experiments was defined as 0 ppm. As the major enantiomer provides ^{125}Te NMR signals to the left or to the right side of the signals due to the minor isomer, depending on the enantiomeric excess of menthol, the enantiomeric excess of menthol was plotted against the ^{125}Te NMR shift as shown in Figure 4. This methodology eliminates the need for an internal or external reference.

3. Conclusion

The results presented herein suggest that the behavior of chiral tellurium ferrocenes can be exploited in the development of new ^{125}Te NMR sensitive environmental probes with potential application in chiral recognition. This behavior suggests a new type of NMR determination of enantiomeric purity, where the chiral organic compound under investigation acts as a chiral solvating agent and the chiral tellurium ferrocene is the subject of the NMR analysis. Work is currently in progress to establish the scope and limitations of this newly observed property of organotellurium compounds. New chiral tellurium ferrocenes are under preparation for this end.

4. Experimental

4.1. General

4.1.1. Materials. All reagents and solvents used were previously purified and dried as reported in the literature.[13] THF was distilled from sodium/benzophenone under nitrogen immediately before use. *n*-Butyllithium and *t*-butyllithium were titrated using 1,10-phenantholine as the indicator prior to use. Column chromatography separations were performed with Merck 60 (70–230 mesh) silica gel. Elemental tellurium of 200 mesh, (*S*)-(+)-*N*-(3,5-dinitrobenzoyl)-α-methyl-benzylamide and (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-α-methyl-benzylamide were purchased from Aldrich Chemical Co. Ferrocene was purchased from Acros Organics.

4.1.2. Analysis. ^{1}H, ^{13}C NMR and ^{125}Te spectra were obtained on a Bruker AVANCE 400 spectrometer, operating at 9.4 T, observing ^{1}H at 400.13, ^{13}C at 100.61 and ^{125}Te at 126.3 MHz. All ^{1}H and ^{13}C spectra were taken in $CDCl_3$ and the chemical shifts are given in ppm related to tetramethylsilane (TMS) as an internal reference, while ^{125}Te NMR spectra were obtained in CH_2Cl_2 at 273 K and diphenyl ditelluride $(PhTe)_2$ in $CDCl_3$ as an external standard ($\delta = 422.0$ ppm). The temperature in the ^{125}Te NMR experiments was accurately kept at 273 K by using a nitrogen gas system and a $\pi/2$ pulse sequence with decoupling only during the acquisition time to produce a minimal sample heat during the measurements was used.

4.2. Typical procedures

4.2.1. Preparation of (±)-*N*,*N*-diisopropyl-(2-butyltellurium)-ferrocenyl-carboxiamide (±)-2.[6,7] To a 100 mL two necked round-bottomed flask equipped with magnetic stirring under a nitrogen atmosphere at −78 °C were added TMEDA (20 mmol) and THF (10 mL). To the solution was slowly added *n*-butyllithium (20 mmol, 2 mol/L in hexane). To the resulting solution was added dropwise a solution of *N*,*N*-diisopropyl ferrocenecarboxiamide (10 mmol,

3.13 g) in THF (20 mL). The mixture was stirred at −78 °C for 1 h. During this period the formation of a red precipitate was observed. After this, it was added dropwise to a mixture a solution of *n*-butyl tellurenyl bromide (10 mmol 2.65 g) in benzene (5 mL). During the addition, the precipitate disappeared. The mixture was stirred at −78 °C for 15 min, and then for 15 min at room temperature. The reaction mixture was quenched with a saturated solution of NH_4Cl (50 mL). The mixture transferred to a separatory funnel and the aqueous phase extracted with ethyl acetate (3×15 mL). The organic phases were combined, dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by column silica gel chromatography eluting with hexane/ethyl acetate (85:15) to give *N*,*N*-diisopropyl-(2-butyltellurium)-ferrocenyl-carboxiamide (±)-**2**, as a red oil. Yield: 4.34 g, (87%); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 0.91 (t, 3H, $J = 7.3$ Hz); 1.62–1.00 (m, 12H); 1.76 (hept, 2H, $J = 6.8$ Hz); 2.70 (t, 2H, $J = 7.3$ Hz); 4.23 (s, 5H); 4.28 (t, 1H, $J = 2.3$ Hz); 4.35 (dd, 1H, $J = 1.0$ Hz, $J = 2.3$ Hz); 4.41 (dd, 1H, $J = 1.0$ Hz, $J = 2.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 168.2; 89.1; 75.2; 71.3; 69.6; 67.5; 50.9; 33.9; 25.0; 20.9; 13.3; 6.9. ^{125}Te NMR (126 MHz, CH_2Cl_2, ppm): δ 316.4.

4.2.2. Preparation of (+)-*N*,*N*-diisopropyl-(2-butyltellurium)-ferrocenyl-carboxiamide (+)-2.[6,7] This compound was prepared using the same procedure used above, but substituting TMEDA for (−)-sparteine (20 mmol).

Acknowledgements

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